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Possible presence of undiagnosed asthma in children in Japan

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KEYWORDS
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Abstract
Background: Asthma diagnosis in children is occasionally challenging, and the issue of undiagnosed asthma before adolescence has been poorly studied in Japan. The present study was conducted to investigate the possible presence of undiagnosed asthma in the general population of children living in a rural area of Japan.
Methods: The participants comprised 120 fourth graders aged 9-10 years (boys/girls: 63/57) attending five elementary schools in Yawatahama, Ehime, Japan. All the children underwent respiratory function tests and fraction of exhaled nitric oxide (FeNO) measurements. Based on the results of a questionnaire, the children were also categorized into groups depending on their allergic diseases.

The authors assessed the results of both the respiratory function tests and the FeNO measurements for children who were classified into the nonallergic group.
Results: A total of 76 (63%) children, who completed the tests appropriately, were included in the analysis. According to the report, among the 24 children in the nonallergic group, six (25%) showed abnormalities in respiratory tests. One had an abnormal % forced vital capacity (%FVC; <80%), three had abnormalities in both forced expiratory volume in 1 sec (FEV1)/FVC (<80%) and % maximal mid-expiratory flow (<65%), three had concave flow-volume curves, and one had a high FeNO measurement (41 ppb).
Conclusion: A certain proportion of Japanese elementary school children, categorized as having no allergy, showed respiratory function test abnormalities. A follow-up study is needed to determine the prognosis and outcomes of the children with these abnormalities.

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Introduction

Bronchial asthma is diagnosed based on a history of repeated paroxysmal wheezing, shortness of breath, and cough, in addition to changes in airflow limitation as revealed by pulmonary function tests.[1] In addition to pulmonary function tests, objective indices such as measurements of fraction of exhaled nitric oxide (FeNO) are also useful to diagnose eosinophilic asthma.[2] For children, however, in addition to the difficulties in performing the tests themselves, the symptoms of asthma can sometimes be difficult to discover due to the children's poor awareness of respiratory symptoms and underreporting of symptoms.[3] It has been reported that 20–73% of people with asthma outside Japan remain undiagnosed.[4] Even in mild cases, abnormal respiratory function in school-age children and delayed preventive treatment for them has been reported to be associated with respiratory dysfunction in their adulthood.[5,6] Therefore, it is important to detect asthma in children with mild or latent cases, during its early stages, to provide appropriate interventions. Although respiratory function tests for potential patients with asthma have been reported,[3,7-11] the current status of children with undiagnosed asthma has not yet been fully determined in Japan, leaving their prognosis largely unknown.

In this study, the authors conducted a survey and performed respiratory function tests for a small sample size consisting of elementary school fourth graders in Yawatahama, Ehime, to investigate whether there were children with undiagnosed asthma in Japan. Yawatahama is a local city with a population of 33,172, located at the base of the Sadamisaki Peninsula at the west end of Ehime.[12]

Participants and methods

Participants

Out of 121 elementary school fourth graders belonging to five elementary schools in Yawatahama, Ehime, a survey, respiratory function tests, and FeNO measurements were conducted on a total of 120 children, including 63 boys and 57 girls, for whom written consent was obtained from their parents for their participation in the study. After analysis of the data, the authors sent brief summaries to all participants individually.

Questionnaire on allergic diseases and their categorization

A questionnaire was prepared based on that used by Nishima et al. in "A Study on the Prevalence of Allergic Diseases in School Children in Western Districts of Japan – Comparison between the Studies in 1992, 2002, and 2012 with the Same Methods and Same Districts."[13] The questionnaires were distributed to the children through the schools, and their parents were asked to complete the forms within approximately 10 days. The final recovery rate of the questionnaires was 100%.

"Asthma," "remission of asthma," and "wheezing" were categorized based on respiratory symptoms (Table 1).

"Allergic rhinitis" was defined as answering "Yes" when asked, "Have you ever been diagnosed as having allergic rhinitis or rhinitis due to hay fever?" and also answering "Yes" to "Do you still have those symptoms (sneezing, runny nose, stuffy nose, etc.)?" or "Are the symptoms strong from February to April?" "Remission of rhinitis" was defined as answering "Yes" only to the first question regarding past diagnosis.

"Allergic conjunctivitis" was defined as answering "Yes" when asked, "Have you ever been diagnosed as having allergic conjunctivitis or hay fever conjunctivitis?" and also answering "Yes" to "Do you still have those symptoms (eye itching, redness, tears, etc.)?" or "Are the symptoms strong from February to April?" "Remission of conjunctivitis" was defined as answering "Yes" only to the first question regarding past diagnosis.

Regarding "atopic dermatitis" and "food allergy," the children who were diagnosed by physicians and were showing symptoms were defined as having the disease, and those who had ever been diagnosed but were showing no symptoms were categorized as being in remission.

Table 1 Questionnaire.

Asthma	1) Has your child ever had an attack of wheezing or whistling that has caused shortness of breath?
	2) Has he/she ever had two or more of such episodes?
	3) Has a doctor ever said that your child has asthma, asthmatic bronchitis, or childhood asthma?
	4) On that occasion, was his/her chest sounding wheezy or whistling?
	5) At that time, did he/she have difficulty in breathing accompanied by wheezing or whistling?
	6) In the past 2 years, has he/she ever received treatment for asthma, asthmatic bronchitis, or childhood asthma?
Wheezing	7) Has his/her chest ever sounded wheezy or whistling more than twice?
	8) Did these wheezing/whistling sounds occur when your child had a cold?
	9) In the past 2 years, has his/her chest ever sounded wheezy or whistling more than twice?

Those who answered "Yes" to all Questions, 1–6, were considered to have asthma.
Those who answered "Yes" to Questions 1–5 and "No" to Question 6 were considered to have asthma remission.
Those who did not correspond to asthma or asthma remission categories and answered "Yes" to Questions 7–9 were considered to have wheezing.

Respiratory function tests and FeNO measurement

During the 2 months from November to December 2015, each elementary school was visited by a team of two physicians and two nurses. The period from November to December with the least pollen dispersal was chosen to minimize the impact of hay fever on respiratory function tests. The tests were conducted in the order of FeNO measurement and then spirometry on the same day for each school. There was no user of inhaled corticosteroids among the participant children. One child was taking steroid nasal drops. All drugs, including internal medicines such as antiallergic drugs and cold remedies, were withdrawn for at least 3 days before the testing.

NIOX MINO® (Chest M. I. Inc., Tokyo, Japan) was used for the FeNO measurements. A spirometer HI-105T (Chest M. I. Inc.) was used for measuring forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC, peak expiratory flow (PEF), and maximal mid-expiratory flow (MMF). For determinations of %FVC, %FEV1, %PEF, and %MMF, the authors used a predictive formula, developed by the Pulmonary Function Committee of the Japanese Society of Pediatric Pulmonology in 2008.[14] Measurements were performed by one physician, taking two measurements per participant. An acceptance criterion, obtained by simplifying the criterion of Miller et al.[15], was used to determine the validity of measurements in flow-volume curves (Table 2). The presence of artifacts was judged by two physicians, including the one who performed the examination.

Statistical analysis

GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA) was used for the statistical analyses. Measurements of flow-volume curves were represented by mean ± standard deviation and FeNO measurements by median (minimum–maximum). A one-way analysis of variance or Kruskal–Wallis test was used for the comparison among three or more groups, and a t-test or a Mann–Whitney U-test was used for the comparison between two groups. Differences with $p < 0.05$ were considered statistically significant.

Ethical considerations

This study was approved by the Ethics Committee of Yawatahama City General Hospital (approval number: 20151020-001). Written consent documents were obtained from the children's parents after explaining that the test results would be used for research purposes only and that care would be taken to avoid the identification of individuals.

Results

Allergic diseases and respiratory function tests

Results of the flow-volume curve for 76 participants (41 boys and 35 girls), accounting for 63% of the children, met the criteria. Subsequent analyses were performed on these children. The prevalence of allergic diseases are shown in Table 3. Characteristics of children in the asthma group are described in Table 4.

In addition to groups of "asthma," "remission of asthma," and "wheezing," children who did not belong to these three groups were further categorized into "allergic group without asthma/wheezing" who had any one of the allergic diseases (including those of remission) and "nonallergic group" who had none of the allergic diseases (including those of remission).

As a result, no significant difference was found in any indices between the five groups (Table 5). A comparison between the two groups, the asthma/wheezing group

Table 2 Examination of acceptable spirograms.

Items to determine	Criteria for determination
1. Artifact	Free from the following artifacts: • Cough • Leak • Glottal closure • Poor effort • Early termination of breathing effort • Mouthpiece obstruction
2. Start of breathing	Extrapolated volume is <5% of FVC
3. End of breathing	Can breathe out for >3 sec or unable to maintain breathing
The tests are considered properly completed when criteria 1–3 are met.	

FVC, forced vital capacity.

Table 3 Prevalence of allergic diseases.

	Boys n = 41	Girls n = 35	Total (prevalence, %)
Bronchial asthma	2	3	5 (6.6)
Remission of bronchial asthma	2	1	3 (3.9)
Wheezing	2	2	4 (5.3)
Allergic rhinitis	13	15	28 (32.9)
Remission of allergic rhinitis	4	1	5 (6.6)
Allergic conjunctivitis	9	10	19 (25)
Remission of allergic conjunctivitis	4	6	10 (13.2)
Atopic dermatitis	7	4	11 (14.4)
Remission of atopic dermatitis	2	2	4 (5.3)
Food allergy	1	1	2 (2.6)
Remission of food allergy	5	2	7 (9.2)

Table 4 Characteristics of children in the asthma group.

Case	Sex	Severity	Allergic rhinitis	Atopic dermatitis	Family history	FeNO (ppb)
A	M	Intermittent			Father: AR Brother: BA, AR	11
B	F	Mild persistent			Mother: AR Brother: BA	7
C	M	Intermittent	○			43
D	F	Intermittent	○	○	Brother: BA	44
E	F	Intermittent	○	Remission	Mother: BA, AD	58

Severity is based on the Japanese guidelines for childhood asthma 2020.[16] None of the children had a history of rhinitis. M: male, F: Female, BA: bronchial asthma, AR: allergic rhinitis, AD: atopic dermatitis

Table 5 Respiratory function and FeNO in each group.

	Asthma group	Remission of asthma group	Wheezing group	Allergic group without asthma/wheezing	Nonallergic group	p
N (boys/girls)	5 (2/3)	3 (2/1)	4 (2/2)	40 (24/16)	24 (11/13)	
Height (cm)	134.4 ± 6.9	131.5 ± 2.6	132.2 ± 4.0	136.3 ± 5.1	137.8 ± 6.8	0.14
%FVC (%)	95.2 ± 10.6	99.8 ± 4.5	98.8 ± 10.0	100.1 ± 10.4	100.0 ± 9.3	0.90
%FEV1 (%)	93.3 ± 10.5	97.1 ± 7.1	94.5 ± 6.5	95.1 ± 10.4	95.4 ± 9.5	0.97
FEV1/FVC (%)	85.4 ± 8.8	95.8 ± 2.7	91.9 ± 5.1	91.8 ± 7.3	90.9 ± 7.5	0.35
%PEF (%)	96.9 ± 18.4	102.7 ± 11.0	109.4 ± 14.9	102.5 ± 16.9	106.0 ± 15.7	0.61
%MMF (%)	72.8 ± 21.2	104.4 ± 22.1	99.6 ± 13.5	89.3 ± 22.3	90.4 ± 21.7	0.29
FeNO (ppb) Median (range)	43 (7-58)	12 (7-24)	51 (9-60)	14 (4-158)	12 (6-41)	0.26

FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMF, maximal mid-expiratory flow; PEF, peak expiratory flow.

(12 children) and the non-asthma/wheezing group (64 children), revealed no significant differences either.

Measurements of flow-volume curves are represented as mean ± standard deviation and FeNO measurements by median (minimum-maximum). A one-way analysis of variance is used, and differences with $p < 0.05$ are considered statistically significant.

Allergic diseases and FeNO

Considering the influence of the presence or absence of allergic rhinitis, the children's FeNO measurements were categorized into four groups: "BA+ AR+," having both asthma/wheezing (combined asthma, asthma remission, and wheezing) and allergic rhinitis; "BA+ AR−," having only asthma/wheezing; "BA−AR+," having only allergic rhinitis; and "BA− AR−," having neither asthma/wheezing nor allergic rhinitis. The number of participants in each group were 8, 4, 20, and 44,respectively, and the median FeNO measurements (minimum-maximum) were 44.5 (7-60), 11.5 (7-24), 15.5 (5-158), and 12.5 (6-66) ppb, in the BA+ AR+, BA+ AR−, BA− AR+, and BA− AR− groups, respectively. There were no significant differences in the FeNO measurements between the groups; however, those of the BA+ AR+ group tended to be high (Figure 1). Meanwhile, the FeNO measurements in the BA+ AR− and BA− AR+ groups with only asthma/wheezing and allergic rhinitis, respectively, were similar to those in the BA− AR− group having neither of them (Figure 1). No differences were observed in the measurements of the flow-volume curves between groups.

Respiratory functions and FeNO in the nonallergic group (Table 6)

The results of questionnaire showed that 24 children (11 boys and 13 girls) had no allergic diseases, including those in remission. Of these 24 children in the nonallergic groups, 6 (25%) showed some test abnormalities. They included one showing %FVC < 80%, three having FEV1/FVC < 80% and %MMF < 65%, three showing concave flow-volume curves (Figure 2), and one with FeNO > 35 ppb. According to the results of the questionnaire, four out of the six children had a family history of allergic diseases. In addition, two out of the three children showed abnormalities in FEV1/FVC and %MMF showed concave flow-volume curves. The child with an abnormal FeNO had a family history of asthma.

The flow-volume curves are shown as well as the height, sex, respiratory function test values, and FeNO measurements of children H, I, and K who had concave flow-volume curves among those exhibiting test abnormalities are listed in Table 6.

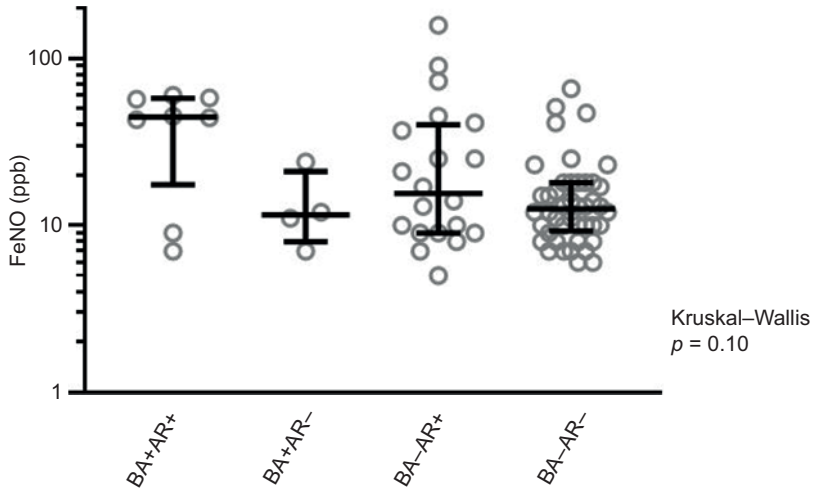


Figure 1 Presence or absence of asthma wheezing/allergic rhinitis and FeNO measurements. "BA+" and "BA−" indicate participants who were included and excluded, respectively, in the "asthma/wheezing group." "AR+" and "AR−" indicate participants with and without allergic rhinitis, respectively.

Table 6 Characteristics of infants with test abnormalities.

Case	%FVC <80%	FEV1/FVC <80%	%MMF <65%	FeNO >35 ppb	Concave flow-volume curve	Family history
F	79.3	89.72	73.3	18		None
G	106.4	72.7	53	7		Brother: BA, father: AR
H	95.7	79.5	58.8	17	○	None
I	92.7	77.1	56.8	12	○	Father and sister: AD, mother: AR
J	102.9	94.89	129	41		Brother: BA
K	101	82.35	76.1	18	○	Mother: AR

AD, atopic dermatitis; AR, allergic rhinitis; BA, bronchial asthma; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMF, maximal mid-expiratory flow.

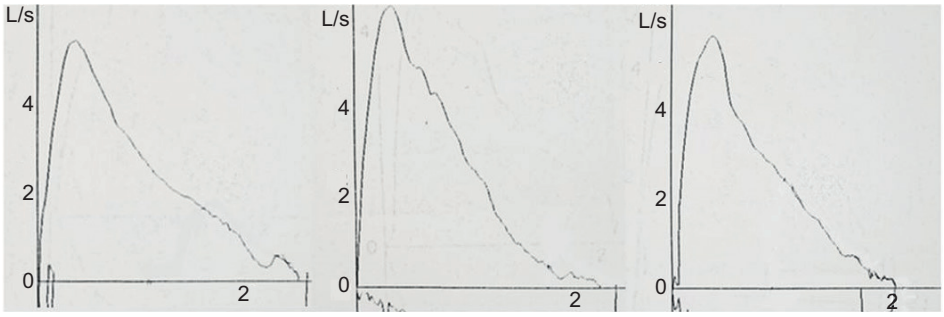
Discussion

The authors performed some respiratory function tests and compared the results by categorizing children based on some allergic diseases. No significant differences were observed unexpectedly. The authors speculate that this result was partly due to inclusion of children with abnormal respiratory function test in the "nonallergic group."

Of the children considered to have no allergic disease, including anamnesis in the questionnaire-based categorization, 25% were found to have abnormalities by performing respiratory function tests or FeNO measurements. In particular, they included three children who had low %MMF, which reflects the status of the peripheral airway and has been reported to be a predictor of the severity of asthma and its exacerbation,[17] and low FEV1/FVC, which further reflects the severity of asthma.[18] Two of these three children showed concave flow-volume curves.

Although there has been no report on children with undiagnosed asthma in Japan as far as we found, the proportion of people with undiagnosed asthma overseas has been reported to be 2–5% in adults[8-10] and 5–8% in children.[11,19] The present survey, which was conducted in a community, suggests that there is a certain rate of children with undiagnosed asthma in Japan, although we did not conduct additional interviews or tests on asthma symptoms for children who showed test abnormalities. The fact that four out of six children who showed test abnormalities had family history of allergic diseases useful for asthma diagnosis[1] appears to reinforce the possibility that they could have included children with undiagnosed asthma. Furthermore, these six children had no history of severe respiratory disease, chronic lung diseases, cardiac problems, and immune deficiency, which may cause abnormal respiratory function tests.

It has been reported that the quality of life of children with undiagnosed asthma and their parents decreases similar to those children with diagonsed asthma.[11] In bronchial asthma, the absence of prophylactic treatment and delayed treatment are considered to be the risk factors for the transition to adult asthma.[6] In addition, test abnormality of respiratory function in children is known to be a predictor of respiratory dysfunction in their adulthood.[5] Thus, the authors believe that it is important to detect children with bronchial asthma, showing test abnormalities at early stages, and to provide them with appropriate interventions. This goal led the authors to plan a similar survey and respiratory function tests for the same participant children



Case H		Case I		Case H	
Height	151 cm	Height	143.5 cm	Height	133.4 cm
Sex	Female	Sex	Male	Sex	Male
%FVC	95.7%	%FVC	92.7%	%FVC	101%
$\%FEV_1$	85.5%	$\%FEV_1$	81%	$\%FEV_1$	94.4%
FEV_1/FVC	79.51%	FEV_1/FVC	77.1%	FEV_1/FVC	82.4%
%PEF	101%	%PEF	122%	%PEF	128.7%
%MMF	58.8%	%MMF	56.8%	%MMF	76.1%
FeNO	17 ppb	FeNO	12 ppb	FeNO	18 ppb

Figure 2 Respiratory function test values for children with abnormal flow–volume curves. FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMF, maximal mid-expiratory flow; PEF, peak expiratory flow.

5 years later, in particular, to investigate the effects of the abnormalities found in this article on their subsequent respiratory function.

There are several criteria for setting the cutoff value of FeNO in the diagnosis of bronchial asthma. In this article, the authors chose 35 ppb, which is reported in the clinical guidelines of the American Thoracic Society,[2] to reduce false positives. The guideline states that eosinophilic airway inflammation is more likely to be present in the children with an FeNO of 35 ppb or higher. The child who showed an FeNO of 41 ppb in the nonallergic group in this article could have subclinical eosinophilic airway inflammation because their sibling had a history of bronchial asthma. In the BA-AR- group, there were four children with abnormal FeNO measurements, including Case J in Table 6. Except for Case J, one child had a history of allergic rhinitis and atopic dermatitis, another had current atopic dermatitis, and the third one had allergic conjunctivitis and a history of sinusitis, as well as suspected eosinophilic airway inflammation based on the questionnaire. These features may have affected the FeNO measurement.

The prevalence obtained in this survey was 6.6% for bronchial asthma, 3.9% for remission of asthma, 5.3% for wheezing, 32.9% for allergic rhinitis, and 6.6% for remission of allergic rhinitis. A similar survey reported by Nishima et al. had shown that the prevalence of each disease among elementary school fourth graders in Japan was 4.76% for bronchial asthma, 2.76% for remission of bronchial asthma, 4.42% for wheezing, 30.15% for allergic rhinitis, and 6.36% for allergic rhinitis remission.[13] Subtle differences in the prevalence of the disease and gender of the participants in this study and the previous report could have been due to the small sample size and regional differences. Although the present study was conducted on a small number of individuals in a community, the prevalence of each disease was generally consistent with that of the previous report, suggesting that the characteristics of the participants in this study were not significantly different from those of the average Japanese population of the same age.

In order to perform credible pulmonary function tests and carry out a second surveillance 5 years after the initial study, fourth graders were targeted. Education up to the 9th grade is compulsory in Japan. The authors were not able to perform these tests on another day and confirm their reproducibility. However, multiple spirometry on the same children confirmed that the tendencies observed were the same. Additionally, the authors set rigorous criteria to assess whether spirometry was performed properly (Table 2). As a result, 63% of the children met the criteria and were included in the study. Although the authors had to complete the tests within a limited time, they considered it necessary to improve the tests by conducting them carefully and spending more time on them, given the presence of a study reporting that 65% of preschool children could receive effective examinations even for the first time.[20] The response rate of 100% to the questionnaire means it is free of nonresponse bias, whereas a limitation is that the participants were the children from only one grade of the local elementary schools. A large-scale study involving urban areas is needed to evaluate the outcomes of the children with test abnormalities.

Conclusion

This study suggests that a certain number of children will show abnormalities in respiratory function tests, even if they appear to have no allergic disease. Further study

is needed to determine the relationship between these test abnormalities and undiagnosed asthma, as well as on the prognosis and outcomes of the children with test abnormalities.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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